

## USE OF IL-10 TO TREAT INFLAMMATORY BOWEL DISEASE

### BACKGROUND OF THE INVENTION

The invention relates generally to manipulation of the human immune response to ameliorate or alter signs or symptoms of inflammatory conditions or diseases relating to inflammation, immunity, or autoimmunity. More specifically, the invention relates to treatment of inflammatory bowel disease using interleukin-10 (IL-10).

The immune system is diverse and complex. It includes a multitude of natural and adaptive immune mechanisms and reactions. For practical purposes, the immune system is often thought of in terms of either humoral and cellular immune responses. Humoral immunity refers broadly to antibody production and actions by B-cells including plasma cells. Cellular immunity is mediated by cells including T-cells, monocytes, macrophages and histiocytes. T-cells and B-cells are two broad categories of lymphocytes. T-cells may be further categorized according to their various functions or markers. For instance, T-cells can be classified as T helper cells or T suppressor cells. Additionally, T-cells can be activated to become cytotoxic or to perform other more specialized functions. Normally, T-cells and B-cells have interactions that may regulate each other's activity to some extent. See, e.g., Paul (ed.) *Fundamentals of Immunology* (2d ed.) Raven Press, New York (1989).

For instance, for different antigens either cellular or humoral responses may predominate, typically, in a mutually exclusive fashion. The severity of some diseases, e.g., leprosy, leishmaniasis, and some types of autoimmunity, may be due the inappropriate dominance of one class of response over the other. Mosmann et al., *Immunol. Today* 8:223-227 (1987); Mosmann et al., *Ann. Rev. Immunol.* 7:145-173 (1989); Parish, *Transplant. Rev.* 13:35-66 (1972); and Liew, *Immunol. Today* 10:40-45 (1989).

One of the mechanisms by which the immune system normally regulates itself includes the production of proteins called cytokines. For example, lymphokines are cytokines produced by T-cells and some B-cells, and monokines are cytokines produced by monocytes. Cytokines, which may be glycosylated, mediate numerous immune responses.

IL-10 is a cytokine capable of mediating a number of actions or effects. IL-10 has been isolated from both mouse and human cells and is involved in controlling the immune responses of different classes or subsets of T helper (Th) cells. Th cells can be divided into different subsets that are distinguished by their cytokine production profiles. Th1 T cell clones produce interleukin-2 (IL-2) and interferon- $\gamma$  (IFN- $\gamma$ ) whereas Th2 cell clones secrete IL-10, IL-4, and IL-5, generally following activation by antigens or mitogenic lectins. Both classes of Th cell clones produce cytokines such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-3, and granulocyte-macrophage colony stimulating factor (GM-CSF). A third category of Th cells (Th0) produces IL-2, IFN- $\gamma$ , IL-4, IL-5, TNF- $\alpha$ , IL-3, and GM-CSF simultaneously.

The different cytokine production patterns of Th1 and Th2 cells reflect their helper functions. Th1 cells are predominantly involved in delayed-type hypersensitivity (DTH) responses, whereas Th2 cells are associated with antibody production. Since antibody (Th2

pathways) and DTH (Th1 pathways) responses are often mutually exclusive, Th1 and Th2 cells are thought to have cross-regulatory effects. IFN- $\gamma$  produced by Th1 cells inhibits proliferation of Th2 cells, and IL-10 produced by Th2 cells inhibits cytokine synthesis by Th1 cell clones, especially IFN- $\gamma$  and IL-2 production.

DTH is an example of a cell-mediated immune response. DTH is characterized by edema and cellular infiltration of the tissue, generally by T cells and monocytes and/or macrophages. Some sets of cytokines are separately associated with DTH reactions and humoral immune responses. Cher et al., *J. Immunol.* 138:3688-3694 (1987); and Mosmann et al. (1987 and 1989). Diseases associated with these classes of response may be caused by inappropriate production of associated sets of cytokines.

As an example of inappropriate cytokine production, evidence suggests that excessive production of IFN- $\gamma$  is responsible for major histocompatibility complex (MHC) associated autoimmune diseases. Treatment of such diseases can include manipulation of selected cytokines. See generally International Application No. PCT/US 90/03554, Publication No. WO 9100349, which discloses compositions and use of IL-10 for treatment of diseases relating to imbalanced or inappropriate immune response, and which is incorporated by reference herein.

Because inflammatory responses are often mediated by cytokine activity, agents that could manipulate synthesis of cytokines would be advantageous for therapy of selected diseases. The present invention relates generally to manipulation of cytokine synthesis and specifically to using IL-10 to treat inflammatory bowel diseases such as ulcerative colitis and Crohn's Disease.

Inflammatory bowel disease (IBD) refers to a group of gastrointestinal disorders characterized by a chronic non-specific inflammation of portions of the gastrointestinal tract. Ulcerative colitis and Crohn's Disease are the most prominent examples of IBD in humans. They are associated with many symptoms and complications, including growth retardation in children, rectal prolapse, blood in stools (e.g., melena and/or hematochezia), wasting, iron deficiency, and anemia, e.g. iron deficiency anemia and anemia of chronic disease or of chronic inflammation. The etiology or etiologies of IBD are unclear. See, Wyngaarden and Smith (eds.) *Cecil's Textbook of Medicine* (W.B. Saunders Co. 1985), Berkow (ed.) *The Merck Manual of Diagnosis and Therapy* (Merck Sharp & Dohme Research Laboratories, 1982), and *Harrison's Principles of Internal Medicine*, 12th Ed., McGraw-Hill, Inc. (1991), all of which are incorporated herein by reference.

Ulcerative colitis refers to a chronic, non-specific, inflammatory, and ulcerative disease having manifestations primarily in the colonic mucosa. It is frequently characterized by bloody diarrhea, abdominal cramps, blood and mucus in the stools, malaise, fever, anemia, anorexia, weight loss, leukocytosis, hypoalbuminemia, and an elevated erythrocyte sedimentation rate (ESR). Complications can include hemorrhage, toxic colitis, toxic megacolon, occasional rectovaginal fistulas, and an increased risk for the development of colon cancer.

Ulcerative colitis is also associated with complications distant from the colon, such as arthritis, ankylosing spondylitis, sacroileitis, posterior uveitis, erythema nodosum, pyoderma gangrenosum, and episcleritis. Treatment varies considerably with the severity and